BHS Educational Course on Red Blood Cell Disorders

Acquired hemolytic, megaloblastic and sideroblastic anemias

Daan Dierickx – UZ Leuven
BHS Educational Course – Seminar 2
Hof Ter Musschen, 14th November 2015
## Anemia: classification

<table>
<thead>
<tr>
<th>Microcytosis (MCV&lt;80 fl)</th>
<th>Normocytosis (MCV 80-100 fl)</th>
<th>Macrocytosis (MCV&gt;80 fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Acute blood loss</td>
<td>Ethanol abuse</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Anemia of chronic disease</td>
<td>Folate deficiency</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Bone marrow suppression</td>
<td>Vitamin B12 deficiency</td>
</tr>
<tr>
<td>(late)</td>
<td>Chronic kidney failure</td>
<td>MDS/AML</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>Endocrine dysfunction</td>
<td>Reticulocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug induced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver disease</td>
</tr>
</tbody>
</table>
Acquired anemias

Hemolytic anemia

Megaloblastic anemia

Sideroblastic anemia
Acquired anemias

Hemolytic anemia

Megaloblastic anemia

Sideroblastic anemia
## Hemolytic anemia

<table>
<thead>
<tr>
<th>Extravascular</th>
<th>Intravascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic</td>
<td>Extrinsic</td>
</tr>
<tr>
<td>Congenital</td>
<td>Acquired</td>
</tr>
<tr>
<td>Immune</td>
<td>Non-immune</td>
</tr>
</tbody>
</table>
Hemolytic anemia

• **Intrinsic – congenital**
  – Hemoglobinopathies
  – RBC membrane disorders
  – RBC enzyme disorders

• **Intrinsic – acquired**
  – Paroxysmal nocturnal hemoglobinuria

• **Extrinsic – acquired**
  – Mechanical hemolysis
  – Hemolysis due to chemical and physical factors
  – Hemolysis due to infectious agents
  – Immune mediated hemolytic anemia
Hemolytic anemia

- **AIHA**
  - Autoimmune hemolytic anemia

- **TMA**
  - Thrombotic microangiopathy

- **PNH**
  - Paroxysmal nocturnal hemoglobinuria
AIHA: DAT

Direct Coombs test / Direct antiglobulin test

Blood sample from a patient with immune mediated haemolytic anaemia: antibodies are shown attached to antigens on the RBC surface.

The patient’s washed RBCs are incubated with antihuman antibodies (Coombs reagent).

RBCs agglutinate: antihuman antibodies form links between RBCs by binding to the human antibodies on the RBCs.

Positive test result

Legend
- Antigens on the red blood cells surface
- Human anti-RBC antibody
- Antihuman antibody (Coombs reagent)

Clinical hemolysis

Positive DAT

DAT-positive, no AIHA 96.4 %

DAT-negative AIHA 5-10 %

DAT-positive AIHA

<table>
<thead>
<tr>
<th>AIHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on optimal temperature of Ab-binding</td>
</tr>
<tr>
<td>Warm Ab AIHA</td>
</tr>
<tr>
<td>Cold Ab AIHA</td>
</tr>
<tr>
<td>Mixed Ab AIHA</td>
</tr>
<tr>
<td>Based on presence of underlying disorder</td>
</tr>
<tr>
<td>Primary/idiopathic AIHA</td>
</tr>
<tr>
<td>Secondary AIHA</td>
</tr>
</tbody>
</table>
**AIHA: classification**

<table>
<thead>
<tr>
<th>Warm AIHA</th>
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</tr>
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<tr>
<td></td>
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<td>Cold AIHA</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>• 37°C</td>
<td>• 4°C (up to 37°C, dependent of thermic amplitude)</td>
</tr>
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<td>Cold AIHA</td>
</tr>
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<td>-----------------------------------------------------</td>
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<td>• RBC agglutination</td>
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<td><strong>• Destruction in liver</strong></td>
</tr>
<tr>
<td>**• Idiopathic, SLE, CLL,</td>
<td><strong>• CAD, post-infectious (in particular EBV, mycoplasma)</strong></td>
</tr>
<tr>
<td>lymphoma, medication</td>
<td></td>
</tr>
</tbody>
</table>
AIHA: biochemistry

- Hb?
- Reticulocytes?
- Bilirubin?
- LDH?
- Haptoglobin?
- DAT?
- Peripheral blood?
- Warning signs?
Cold AIHA: treatment

Transient cold AIHA
- Transfusion of packed RBCs if needed
  - Antibiotics in case of definite bacterial infection (*Mycoplasma pneumoniae*)
- Consider a short course (~3 weeks) of corticosteroids in case of severe HA

Chronic cold agglutinin disease
- Avoidance of cold
- Prompt treatment of febrile infections, vaccinations (influenza, pneumococcal) + folinic acid
- Transfusion of prewarmed packed RBCs (transient exacerbation of HA)

Chronic active or relapsing and symptomatic HA?
- Yes
  - Consider treatment with rituximab ± fludarabine
- No
  - No specific treatment is required ("wait and watch")

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<thead>
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<td>AIHA</td>
</tr>
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</tr>
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Hemolytic anemia

- Autoimmune hemolytic anemia (AIHA)
- Thrombotic microangiopathy (TMA)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- **ADAMTS13-deficiency thrombotic thrombocytopenic purpura (TTP)**
  - Acquired (auto-anti-ADAMTS13 antibodies)
  - Congenital (mutations in ADAMTS13 gene)

- **Hemolytic uremic syndrome (HUS)**
  - Typical HUS (Shiga toxin producing Escherichia coli)
  - Atypical HUS
    - Congenital (mutations in complement regulatory proteins, thrombomodulin)
    - Acquired (auto-anti-complement regulatory proteins antibodies)

- **Secondary thrombotic micro-angiopathy (TMA): associated with**
  - Solid organ transplantation
  - Hematopoietic stem cell transplantation
  - Pregnancy
  - Medication (clopidogrel, ticlodipin, quinine, mitomycin C, gemcitabin, calcineurin inhibitors, proliferation signaling inhibitors,...)
  - Auto-immune disorders (antiphospholipid syndrome, systemic lupus erythematosus,...)
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*Image from UZ Leuven*
TTP: symptoms

• Pentade:
  – **Coombs negative hemolytic anemia**
    • Presence of schistocytes
    • Elevated indirect bilirubin
    • Elevated LDH (hemolysis + tissue damage)
  – **Trombocytopenia**
    • In acute phase very low (<20000/µL)
    • Often bleeding tendency
  – **CNS abnormalities**
    • Most frequently: coma, convulsions and focal deficits
    • Often in advanced and non-diagnosed cases
  – **Renal abnormalities**
    • Elevated serum creatinin, microscopic hematuria, proteinuria
  – **Fever**
    • Recently: often cardiac and pancreatic involvement
TTP $\rightarrow$ pentade

Coombs negative hemolytic anemia

Thrombocytopenia

CNS abnormalities

Renal problems
TTP: treatment

• High mortality (>90%) without treatment

• Daily TPE: reduction mortality to <20%
  – Plasma infusion: less effective but value in initial phase if TPE not immediately available

• Substitution fluid: FFP

• Plasmapheresis component: removal of auto-antibodies against ADAMTS13

• Infusion of plasma: contains non-inhibited ADAMTS13

• Recommendations: daily plasma exchange (1-1.5 x plasma volume)

• Duration: daily until platelet normalization during 2-3 consecutive days

• Steroids 1 mg/kg/day (fast tapering)

TTP: why do we need new treatments?

- Suboptimal response
  - Exacerbations (50%)
  - Refractoriness (10%)
- Death: 15%
- During follow up: 15% develop other autoimmune disorder

How to improve outcome of patients with TTP?

• Blocking vWF-platelet binding

• Anti-CD20 therapy
Blocking vWF-platelet binding

Blocking vWF-platelet binding

- GBR 600
- ALX-0681
- ARC1779
- ALX-0081 (caplacizumab)

Callewaert F et al. Blood 2012;120:3603-10
Salles II & Crawley JT. Blood 2012;120:3390-2
TITAN trial

CONVENTIONAL ANTIBODY
Heavy and light chains
Both chains required for antigen binding and stability

HEAVY-CHAIN ANTIBODY
Only heavy chains
Full antigen binding capacity and highly stable

Phase II TITAN design and schedule

**RANDOMISATION**

1:1

**Target**
110 subjects

**Actual**
75 subjects

**Primary endpoint:**
time to confirmed normalisation of platelet count

**Secondary endpoints:**
plasma exchange frequency and volume; relapse; exacerbations; mortality; major clinical events (stroke, MI, organ dysfunction); recovery from signs/symptoms; ADA

**Long-term endpoints:**
ADA; relapse; non focal neurological symptoms

**Safety & efficacy endpoints**

PE
Placebo N=39

PE
Caplacizumab N=36

30 days 30 days

1 year follow-up

1 year follow-up
TITAN trial summary

Strong clinical proof-of-concept

**PRIMARY ENDPOINT**

- Patients treated with caplacizumab achieved confirmed platelet normalisation at more than twice the rate of the group treated with placebo
- This effect was statistically significant \((p = 0.005)\)

**SECONDARY ENDPOINT**

- 71% fewer patients with an exacerbation
- No deaths in the caplacizumab arm compared to 2 deaths in the placebo arm

**SAFETY**

- Increased bleeding tendency (but believed to be manageable)
- Overall, caplacizumab has an acceptable safety profile
**HERCULES trial**

Double-blind Phase III study – design and schedule

**Randomisation**: 1:1

**Primary endpoint**: time to confirmed normalisation of platelet count (measure of prevention of further micro vascular thrombosis)

**TREATMENT PERIOD**

- Daily PE
- Placebo* N=46
- Daily PE
- Caplacizumab* N=46

**FOLLOW-UP PERIOD (4 weeks)**

- Extension of blinded study drug based on ADAMTS13 <10%
  (max 4x7 days)

  If relapse during extension period, restart daily PE and open label caplacizumab

**Secondary endpoints**: exacerbations/relapses; mortality rate; severe morbidity; organ damage biomarkers (troponin, creatinine, LDH); PE parameters; days in ICU/hospital; AEs; PD; PK; immunogenicity

*  iv bolus (10mg) followed by daily sc (10mg)

** incl. corticosteroids at start of daily PE until underlying disease activity resolved
How to improve outcome of patients with TTP?

- Blocking vWF-platelet binding
- Anti-CD20 therapy
Diagnosis of TTP

Start TPE & steroids

Complete remission
Exacerbation
Refractory

Ongoing remission
Normal ADAMTS13
Ongoing remission
Low ADAMTS13
Relapse

Rituximab in TTP

Rituximab in TTP

Diagnosis of TTP

Start TPE & steroids

Complete remission

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Ongoing remission
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Rituximab in TTP

Diagnosis of TTP
- Start TPE & steroids
  - R?

Complete remission
- R?

Exacerbation
- R?

Refractory
- R?

Ongoing remission
- Normal ADAMTS13
  - R?

Ongoing remission
- Low ADAMTS13
  - R?

Relapse
- R?

Rituximab in TTP

Diagnosis of TTP

Start TPE & steroids

Complete remission

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Ongoing remission

Low ADAMTS13

Relapse

How to improve outcome of patients with TTP?

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  - Auto-immune disorders (antiphospholipid syndrome, systemic lupus erythematosus,...)
Complement cascade

Atypical HUS

<table>
<thead>
<tr>
<th>Factor mutated</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement factor H (CFH)</td>
<td>20-30%</td>
</tr>
<tr>
<td>Membrane cofactor protein (MCP = CD46)</td>
<td>5-15%</td>
</tr>
<tr>
<td>Complement factor I (CFI)</td>
<td>4-10%</td>
</tr>
<tr>
<td>Thrombomodulin (THBD)</td>
<td>3-5%</td>
</tr>
<tr>
<td>C3</td>
<td>2-10%</td>
</tr>
<tr>
<td>Complement factor B (CFB)</td>
<td>1-4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Auto-antibodies</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CFH</td>
<td>6%</td>
</tr>
</tbody>
</table>

Loirat C, Frémeaux-Bacchi V. Orphanet J Rare Dis 2011;6:60
Atypical HUS

Prognosis of aHUS Varies According to the Genetic Defect
Noris M et al, CJASN 2010

ESRD or Death

250 patients
Age at onset: birth to 83 years

Cumulative Event-Free Survival (%)

Months After Onset

The majority of patients received some form of plasma therapy

Atypical HUS

Atypical HUS

Eculizumab

Kavanagh D, Goodship T. Pediatr Nephrol 2010;25:2431-42
Eculizumab in aHUS
– Two prospective phase 2 trials

Eculizumab in aHUS

Eculizumab – Approved Dosing Schedule in aHUS

For patients ≥18 years of age, eculizumab therapy consists of:

<table>
<thead>
<tr>
<th>Patient Body Weight</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1200 mg at week 5; then 1200 mg every 2 weeks</td>
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<tr>
<td>30 kg to less than 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
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<tr>
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<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
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<td>300 mg at week 2; then 300 mg every 3 weeks</td>
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For patients <18 years of age, administer eculizumab based upon body weight, according to the following schedule:

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For patients ≥18 years of age, eculizumab therapy consists of:
Conclusion

Transplant associated

Complement therapy

Acquired TTP

Blocking vWF-BP
Rituximab

Congenital TTP

rhADAMTS13

Atypical HUS

Eculizumab

Transplantation

Eculizumab
(German outbreak
E.coli
0104:H4)

Complement

Complement

Plasma

TMA

ADAMTS13

Typical HUS

rhADAMTS13
<table>
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<th>TMA</th>
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<tr>
<td>Intrinsic</td>
<td>TMA</td>
</tr>
<tr>
<td>TMA (TTP, aHUS)</td>
<td>TMA</td>
</tr>
<tr>
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Hemolytic anemia

- AIHA: Autoimmune hemolytic anemia
- TMA: Thrombotic microangiopathy
- PNH: Paroxysmal nocturnal hemoglobinuria
intravascular hemolytic anemia

PNH

bone marrow failure
(cytopenias)

thrombosis
Sr William Gull (London, 1866) : « anemic young tanner suffering from morning crises of intermittent haematinuria »

- **It’s not paroxysmal**
  
  Even in the absence of symptoms, progression of disease is ongoing

- **It’s not nocturnal**
  
  Hemolysis in PNH is subtle and constant, 24 hours a day

- **Hemoglobinuria is a a less common observed complication**
  
  ¾ patients present without hemoglobinuria

defect in the GPI anchor
1) **classical PNH**: evidence of PNH in the absence of another bone marrow disorder

2) **PNH in the setting of another specified bone marrow disorder** (e.g. MDS-RA, AA, myelofibrosis)

3) **subclinical PNH**: PNH abnormalities on flow cytometry without signs of hemolysis

Thrombosis is the Leading Cause of Death in PNH

• Up to 44% of patients experience clinical thrombotic events (venous 85%)

• Thrombosis in PNH can be life-threatening
  ➢ 40-67% of deaths are due to thrombosis
  ➢ first thrombotic event can be fatal
  ➢ first TE increases risk for death 5 to 10-fold

• Occurs in typical and atypical sites

• Is not adequately managed with anticoagulation

• unpredictable

Atypical sites

- Abdominal (splanchnic, mesenteric, Budd-Chiari), cerebral thrombosis (sagittal sinus), CVA at young age, dermal thrombosis.

Typical sites, including one or more of the following:

- Prior thrombo-embolism in typical sites
- Evidence of hemolysis
- Accompanying bone marrow failure disorder
- While receiving anticoagulant therapy
- Pancytopenia

Transfusions
  - Risk of iron overload
  - Transient treatment of anemia

Anticoagulants
  - Risk of hemorrhage
  - Ineffective in many patients

Red cell supplements
  - Folic acid, iron, erythropoiesis-stimulating agents

Steroids/androgen hormones
  - No controlled clinical trials
  - AE’s

Supportive Care Options Do Not Impact Progression and Risk for Severe Morbidities and Mortality

PNH: eculizumab

Pilot Study – *NEJM.* 2004
N=11
Primary endpoint: reduction of hemolysis

TRIUMPH – *NEJM.* 2006
Pivotal Phase III, Double-Blind, Placebo-Controlled Trial, N=87

SHEPHERD – *Blood.* 2008
Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N=97

Long-Term Extension Trial
Hillmen – *Blood.* 2007
Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to Soliris
N=187
# PNH: eculizumab

<table>
<thead>
<tr>
<th>TRIUMPH</th>
<th>Placebo group</th>
<th>Eculizumab group</th>
<th>SHEPHERD</th>
<th>Extension† (all studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, no.</td>
<td>44</td>
<td>43</td>
<td>97</td>
<td>195</td>
</tr>
<tr>
<td>TE events, no.</td>
<td>11</td>
<td>16</td>
<td>91</td>
<td>124</td>
</tr>
<tr>
<td>Patient-years, no.</td>
<td>470.4</td>
<td>309.0</td>
<td>718.3</td>
<td>1683.4</td>
</tr>
<tr>
<td><strong>TE event rate, no. per 100 patient-years</strong></td>
<td>2.34</td>
<td>5.18</td>
<td>12.67</td>
<td>7.37</td>
</tr>
<tr>
<td><strong>Eculizumab treatment‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>195</td>
</tr>
<tr>
<td>TE events, no.</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3§</td>
</tr>
<tr>
<td>Patient-years, no.</td>
<td>22.9</td>
<td>21.8</td>
<td>96.9</td>
<td>291.0</td>
</tr>
<tr>
<td><strong>TE event rate, no. per 100 patient-years</strong></td>
<td>4.38</td>
<td>0.00</td>
<td>2.06</td>
<td>1.07‖</td>
</tr>
</tbody>
</table>

---

**Table 2. Stabilization of Hemoglobin Levels and the Number of Units of Packed Red Cells Transfused during Treatment.**

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Before Treatment</th>
<th>During Treatment</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with stabilized hemoglobin levels (%)</td>
<td>NA</td>
<td>NA</td>
<td>0.0001</td>
</tr>
<tr>
<td>Packed red cells transfused (units/patient)</td>
<td>8.5</td>
<td>9.0</td>
<td>3</td>
</tr>
<tr>
<td>Median</td>
<td>7-12</td>
<td>6-12</td>
<td>6-12</td>
</tr>
<tr>
<td>Inquartile range</td>
<td>7-12.3</td>
<td>6-12</td>
<td>6-16</td>
</tr>
<tr>
<td>Mean</td>
<td>9.5±0.7</td>
<td>9.6±0.6</td>
<td>11±0.8</td>
</tr>
<tr>
<td>Total</td>
<td>437</td>
<td>413</td>
<td>482</td>
</tr>
</tbody>
</table>


Eculizumab – Approved Dosing Schedule in PNH

For patients \(\geq 18\) years of age, eculizumab therapy consists of:

<table>
<thead>
<tr>
<th>Patient Body Weight</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq 40) kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1200 mg at week 5; then 1200 mg every 2 weeks</td>
</tr>
<tr>
<td>30 kg to less than 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20 kg to less than 30 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3; then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg to less than 20 kg</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg to less than 10 kg</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>

For patients <18 years of age, administer eculizumab based upon body weight, according to the following schedule:
<table>
<thead>
<tr>
<th>Extravascular</th>
<th>PNH</th>
<th>PNH</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
<td>PNH</td>
<td></td>
</tr>
<tr>
<td>Immune</td>
<td></td>
<td></td>
<td>PNH</td>
</tr>
</tbody>
</table>
Acquired anemias

Hemolytic anemia

Megaloblastic anemia

Sideroblastic anemia

Acquired anemias

Hemolytic anemia

Megaloblastic anemia

Sideroblastic anemia

1. Difference between cold and warm AIHA is important as therapy differs.

2. Initial treatment of AIHA consists of steroids and RBC if necessary.

3. Warning signs for sudden deterioration in AIHA: persisting reticulocytopenia, cardiac or neurological symptoms.

4. TTP is an emergency: in case of suspicion always start therapeutic plasma exchange as soon as possible.
5. Current treatment of TTP is associated with a death rate of 15%, making additional treatment strategies (both short and long term) necessary.

6. Eculizumab is standard of care in both atypical HUS and PNH.

7. Thrombosis (often at unusual sites) is the leading cause of death in PNH.

8. In PNH eculizumab reduces thromboembolic event rates and transfusion needs and improves QOL.